Using cohort studies to estimate mortality among injecting drug users that is not attributable to AIDS

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Sex Transm Infect 2006;**82**(Suppl III):iii56–iii63. doi: 10.1136/sti.2005.019273

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Accepted for publication 28 March 2006

Background: Injecting drug use (IDU) and associated mortality appear to be increasing in many parts of the world. IDU is an important factor in HIV transmission. In estimating AIDS mortality attributable to IDU, it is important to take account of premature mortality rates from other causes to ensure that AIDS related mortality among injecting drug users (IDUs) is not overestimated. The current review provides estimates of the excess non-AIDS mortality among IDUs.

Method: Searches were conducted with Medline, PsycINFO, and the Web of Science. The authors also searched reference lists of identified papers and an earlier literature review by English *et al* (1995). Crude mortality rates (CMRs) were derived from data on the number of deaths, period of follow up, and number of participants. In estimating the all-cause mortality, two rates were calculated: one that included *all* cohort studies identified in the search, and one that only included studies that reported on AIDS deaths in their cohort. This provided lower and upper mortality rates, respectively.

Results: The current paper derived weighted mortality rates based upon cohort studies that included 179 885 participants, 1 219 422 person-years of observation, and 16 593 deaths. The weighted crude AIDS mortality rate from studies that reported AIDS deaths was approximately 0.78% per annum. The median estimated non-AIDS mortality rate was 1.08% per annum.

Conclusions: Illicit drug users have a greatly increased risk of premature death and mortality due to AIDS forms a significant part of that increased risk; it is, however, only part of that risk. Future work needs to examine mortality rates among IDUs in developing countries, and collect data on the relation between HIV and increased mortality due to all causes among this group.

The injection of illicit drugs and the mortality and morbidity caused by their use appear to be increasing in many parts of the world.[1 2] Estimating mortality related to illicit drug use is difficult[3] but such estimates are needed because injecting drug use (IDU) clearly has a substantial adverse effect on the health and wellbeing of those who engage in it.[4 5]

One of the most widely discussed causes of death among injecting drug users (IDUs) is AIDS. In 2005, it was estimated that 40.3 million people were living with HIV, and that AIDS had caused 3.1 million deaths in 2005, and 25 million since 1981.[6] Injecting drug use is thought to be the primary factor responsible for the spread of HIV in Eastern Europe and Central Asia.[6] It can account for at least 10% of AIDS cases in many high income countries.[6]

Given the importance of IDU in the transmission of HIV in many areas of the world it is important to have valid estimates of AIDS mortality in this population.[7–10] In deriving these estimates it is also important to take account of the increased premature mortality rate among IDUs, which previous work has suggested is approximately 13 times that of their non-injecting peers.[5 11] It is accordingly important to take account of this increased excess mortality among IDUs that is not attributable to AIDS, to ensure that estimates of AIDS related mortality among IDUs are not overestimated. The current review was completed to provide estimates of this excess mortality among IDUs not attributable to AIDS.

Defining injecting drug use

Injecting drug use may involve the use of a variety of drugs that are prohibited by international law. These drugs most often include: amphetamine-type stimulants, cocaine, heroin, and other opioids. This paper will focus on the mortality related to the use of amphetamines, cocaine, and opioids. Other substances that may be injected (such as benzodiazepines and MDMA (or "ecstasy") have not been included in the present analysis because there is insufficient research to quantify the health risks associated with the injection of these drugs. Newly emerging drugs, such as MDMA, are rarely injected even by those who regularly inject other drugs.[12] The exclusion of these drugs from the current analysis does not mean that the use of these drugs is safe; it simply reflects a paucity of research on the harms caused by their use.

The mortality risks of injecting illicit drug use increase with increasing frequency and quantity of injecting.[13] These harms are most common among dependent drug users who typically inject drugs daily or near daily over periods of years. This pattern of use exposes users to the highest risks of fatal overdose[14] and of contracting blood borne viral (BBV) diseases.[15] As will become clear, most of the evidence on mortality among IDUs comes from cohort studies conducted with people in treatment for their drug use, most of whom will have engaged in these high risk patterns of injecting drug use.

Major causes of death among injecting drug users

Several studies have calculated standardised mortality ratios from cohorts of drug users who been treated in Europe and North America. A meta-analysis of these studies indicated that drug users have mortality rates approximately 13 times higher than their peers.[5 11] The major causes of premature death among illicit drug users were relatively direct consequences of their drug use. There are major problems in using data from cohort studies in a limited number of largely developed countries to derive global estimates of mortality rates among injecting drug users, but in the absence of more representative global data there is no alternative.

Abbreviations: BBV, blood borne virus; BBVI, blood borne viral infections; CMR, crude mortality rates; CNS, central nervous system; HAART, highly active antiretroviral therapy; IDU, injecting drug use; NSP, needle and syringe programmes.

Four main causes of premature death have shown increased rates by comparison with age peers who do not use illicit drugs. These are: drug overdose, AIDS, suicide, and trauma.

Overdose

Overdose from the major illicit drugs can be fatal. Opioids, for example, cause respiratory depression that can cause death. This is especially likely to occur after a period of abstinence and if opioids are used in combination with other central nervous system (CNS) depressant drugs such as alcohol and benzodiazepines.[14 16] Stimulant drugs, such as cocaine and amphetamines, can cause fatal cardiac arrhythmias and strokes,[17 18] which are very rare causes of death in young adults who do not use these drugs.

Suicide

Intoxicating drugs like alcohol and opioids, and dependence on these drugs, have been shown in case control and prospective studies to be strong risk factors for suicide.[19 20] Opioid dependent people in treatment report very high rates of attempted suicide.[21]

Trauma

Trauma includes homicide, motor vehicle accidents, and other forms of accidental death. In the 2000 WHO global burden of disease study it was noted that there are significant problems with estimates of rates or attributable fractions due to trauma, because cohort studies reported different sorts of trauma, and different numbers of causes.[4] In the attributable fraction method of calculation, only road traffic accidents were used to calculate the number attributable to illicit drug use as it is unclear the extent to which homicides or other trauma deaths are due to illicit drug use.[4] Driving while intoxicated by alcohol is a well known risk factor for fatal motor vehicle accidents[11] and heavy alcohol use is common among illicit drug users.[22–24] Opioids are also intoxicating substances that adversely affect driving, although they are much less commonly found in people killed in fatal car crashes. Nonetheless, there is evidence to suggest that drug driving occurs frequently among IDUs.[25]

AIDS

Injecting drug use is an important risk factor for the transmission of blood borne viral infections (BBVI), the most commonly cited of which are the human immunodeficiency virus (HIV) and hepatitis C virus. Good evidence suggests an increased incidence of HIV contracted as a result of sharing of injecting equipment by IDUs in developing societies.[26–29] The connection between illicit drug use and HIV largely arises from injection as the route of drug administration via drug users sharing contaminated injecting equipment.

METHOD

To provide data on the risks of illicit drug use, a series of extensive computer searches was conducted of the following databases: Medline, PsycINFO, PubMed, and the Web of Science. In addition we also searched reference lists of identified papers and an earlier literature review by English *et al*[11] which covered literature published before 1993.

Search terms

1. *Illicit drug*, or *substance use*, or *substance abuse*, or *drug use*, or *drug abuse*, or *heroin*, or *opiates*, or *cocaine*, or *amphetamine*—limited to human studies published in the English language.
2. *Cohort, or case-control*
3. *Mortality*
4. *Morbidity*
5. *Suicide, or accidents, or HIV, or assault*

Strategy: combine 1 and 2; 1 and 3 and 4; 1 and 3 and 5.

Inclusion criteria

The following inclusion criteria were used:

- cohort studies on the use of opioids, cocaine, or amphetamines and mortality;
- studies in which crude mortality rates (CMRs) could be derived from the available data in the article.

Exclusion criteria

The following exclusion criteria were used:

- multiple reports of same data set;
- subsets of a cohort; and
- reviews, commentaries, letters, and abstracts.

English *et al*[11] identified a total of 13 studies investigating mortality associated with illicit opioid use up to 1993.[30–42] Through extensive literature searches a further 20 studies were identified, excluding studies which used previously published data[43–67] (see table 1 for details).

There are a number of general limitations of cohort studies that have been discussed elsewhere.[68–70] There are several that are particularly pertinent here: (a) these studies were conducted exclusively in high income countries (principally the United States with 11 studies, Western Europe with 22 studies, and Oceania with two studies); (b) with one exception[58] these studies drew their samples from people who were identified through seeking treatment for drug related problems; (c) the majority involved opioid users; and (d) the majority of cohort studies were conducted in the pre-AIDS era. The implications of these limitations will be discussed in more detail later.

Approach used

CMRs were derived from data on the number of deaths, period of follow up, and number of participants. Where person-years were not calculated by the authors of a particular paper, those lost to follow up were assumed to be alive at the end of study period and included in our calculation of person-years observation (to maintain consistency with studies that did not report numbers lost to follow up). Following previous research[5] it was assumed that people dying during the period of follow up died in the middle of the period (when estimating the person-years at risk). In calculating weighted mortality rates, all person-years of follow up were summed, as were the deaths due to AIDS and other causes. A 95% error band was calculated as a 95% standard error of the estimate calculation.

CMRs were not adjusted because of the general absence of mortality by age and sex. Instead, mortality was expressed as % mortality by specific cause per annum.

In estimating the all-cause mortality, two rates were calculated: one that included *all* cohort studies identified in the search, and one that only included studies that reported on AIDS deaths in their cohort. This provided lower and upper mortality rates, respectively.

It is important to remember that the majority of the cohort studies were conducted in the pre-AIDS era. This is important in the present circumstances because IDUs with HIV are more likely to die from other causes of mortality than those who are not HIV+.[56] This introduces an additional source of uncertainty in the estimates. Three ways of estimating the rate of mortality other than AIDS have been used in this study to reflect the uncertainty:

Table 1 Cohort studies that examined rates of all-cause and AIDS mortality among drug users

Reference	Year	Site	n	Population studied	Follow up years	Lost	Person-years	Drug	AIDS deaths	AIDS CMR*	Total deaths	Overall CMR*
32	1968	United Kingdom	1272	Heroin addicts known to Home Office	1.8	–	2291	Heroin	NR	NR	85	2.7
30	1968	London, UK	100	Hospitalised male heroin addicts	2.25	–	225	Heroin	NR	NR	13	5.7
42	1973	New York, USA	100	Treatment, male	20	17	1660	Narcotics	NR	NR	23	1.15
101	1979	New York, USA	1156	Treatment (84% methadone)	7	102	8092	Heroin	NR	NR	45	0.56
102	1981	New Haven, USA	91	Treatment	52	–	4732	Morphine	0	0	40	0.84
103	1981	London, UK	128	Treatment (Rx heroin)	10	–	1280	Heroin	NR	NR	19	1.48
39	1982	34 treatment agencies in USA	3324	Treatment	4	–	11 710	Opioids	NR	NR	179	1.52
104	1984	Gothenburg, Sweden	618	Drug using conscripts, rehab & psych patients, drug using welfare recipients	10	–	5789	Cannabis, solvents, LSD, stimulants (opioids rare)	0	0	26	0.45
37	1984	Copenhagen, Denmark	300	Treatment	7	19	1967	Morphine	NR	NR	47	2.40
105	1986	Edinburgh, UK	184	Heroin users attending a general practice	4	4	720	Heroin	0	0	7	0.972
106	1987	18 treatment agencies in USA	697	Treatment	6	142	3330	Opioids	NR	NR	52	1.56
107	1988	Copenhagen, Denmark	300	First time entrants to treatment	11	30	2970	Opioids	NR	NR	78	2.63
108	1988	Lund, Sweden	524	Treatment: opioid, amphetamine, and both opioid and amphetamine	10	0	5240	Opioids, amphetamines	0	0	62	1.18
109	1990	Copenhagen, Denmark	169	Methadone	8	–	1352	Opioids	NR	NR	39	2.88
76	1990	Sweden	368	Methadone and untreated	5–11	–	3283	Heroin	0	0	96	2.92
34	1991	Stockholm, Sweden	1630	Drug related hospitalisation	12		19 560	41% stimulants; 12% heroin; 16% polydrug; 31% other	NR	NR	446	2.3
74	1992	Amsterdam, Netherlands	390	Methadone	2.2	–	810	Opioids	3	0.37	29	3.58
110	1992	Wellington, New Zealand	997	Treatment	9.1	–	9073	Injecting opioid users	0	0	67	0.74
52	1993	Ireland	45	Pregnant on methadone	6	–	270	Opioids	NR	NR	7	2.59
38	1993	California, USA	581	Males in compulsory treatment	24	35	13 064	Narcotics	0	0	161	1.23
53	1993	Oslo, Norway	1009	HIV test centre clients	3.67	–	3706	IDU	4	0.11	87	2.35
54	1994	London, UK	128	Treatment	22	7	2816	Heroin	0	0	41	1.53
55	1994	Edinburgh, UK	203	GP	10	17	2030	IDU	16	0.79	40	1.97
56	1994	Rome, Italy	2431	Treatment	3.2	–	7872	IDU	89	1.13	181	2.30
57	1994	Milan, Italy	2432	Treatment	6.7	–	16 415	Methadone	144	0.88	413	2.52
59	1995	Italy	4962	Treatment	3.88	–	21 130		150	0.71	332	1.57
58	1995	Portland, USA	1769	Not in treatment	1.78	–	3149	IDU	0	0	33	1.05
60	1995	Albuquerque, USA	1013	Treatment	22	243	22 286 (16 940 excl lost)	Methadone	NR	NR	348	1.56 (2.05)
61	1995	Stockholm, Sweden	472	HIV+	3.8	–	1793		7	0.39	69	3.85
62	1996	New York, USA	858	Drug and alcohol dependents on welfare	8	–	6864	Drugs and alcohol	84	1.23	183	2.67
63	1996	Amsterdam, Netherlands	632	HIV: methadone and STD clinic patients	4.4	18	2781		12	0.43	72	2.59
64	1996	Catalonia, Spain	15 711	Hospital ER and treatment	2.8	–	43 717	Opioids	472	1.08	1315	3.01
65	1996	Sydney, Australia	296	Methadone	13	39	3484	Heroin	0	0	42	1.21

Table 1 Continued

Reference	Year	Site	n	Population studied	Follow up years	Lost	Person-years	Drug	AIDS deaths	AIDS CMR*	Total deaths	Overall CMR*
66	1997	Stockholm, Sweden	1494	Hospitalised for drug dependence	22	–	32 868	57% stimulants; 39% opioids			521	1.59
67	1997	Stockholm, Sweden	1640	Drug related hospitalisation	8	0	13 120	14% heroin; 35% amphetamine; 23% polydrug	18	0.14	214	1.63
43	1997	Rome, Italy	3955	Treatment	4	198	15 820	IDU	168	1.06	387	2.45
44	1998	United Kingdom	92 802	"Drug addicts" notified to Home Office	27	–	687 673	65% opioids			5310	0.77
77	1998	Philadelphia, USA	507	Methadone	1	5	507	Heroin	0	0	13	2.56
45	1999	Amsterdam, Netherlands; Baltimore, USA	2809	Treatment shelters and community agencies	6–9	–	15 107	IDU	0	0	264	1.75
46	2000	Catalonia, Spain	135	Treatment	10.5	–	1418	Heroin	21	1.48	41	3.4
51	2001	USA	6570	Methadone	6.7	–	44 019	Heroin	330	0.75	1351	3.07
50	2001	Rome, Italy	11 432	Methadone, other treatment	18	39	80 787	Heroin	715	0.89	1734	2.15
49	2004	Maryland, USA	256	Recent IDU	10	–	2116	IDU	26	1.23	69	3.26
75	2005	Barcelona, Spain	5049	Heroin users entering treatment	8	–	23 048	Heroin	386	1.67	1005	4.36
47	2006	Amsterdam	899	Low threshold methadone	8.8	188	7106	Heroin	94	1.32	183	2.57
48	2006	Valencia, Spain	3247	HIV testing centres	8.6	–	26 772	IDU	281	1.04	585	2.18

CMR, crude mortality rate per 100 person years; NR, these studies did not report on AIDS deaths in their cohort.
–, No data.

1. a rate that is derived from all cohort studies reporting all-cause mortality, reduced by the AIDS mortality rate derived from the subset of studies that report AIDS related deaths;
2. a rate that is derived *only* from cohort studies that reported all-cause mortality *and* AIDS deaths; and
3. a median estimate, which is the midpoint of these two estimates.

It is important to consider that studies not reporting AIDS mortality were conducted either before the AIDS era, or were drawn from populations in which the HIV prevalence among IDU was low. Consequently, the estimate produced by method (1) will produce a lower estimate of mortality than the estimate produced by (2),[56 71] because the latter studies probably included samples with a much higher prevalence of HIV. The median estimate (3) was used to "average" the two.

RESULTS

All-cause mortality

All-cause mortality derived from all cohort studies

A total of 179 885 participants were observed in these cohort studies. There were 1 219 422 person-years of observation, during which time 16 593 deaths were recorded. The weighted average all-cause mortality rate was 1.36% per annum, with a 95% CI of the average rate estimated as between 1.05% and 1.67% per annum.

All-cause mortality derived from cohort studies reporting AIDS deaths

The studies in table 1 were studies that reported on the number of AIDS deaths in their cohorts as well as all cause mortality. In these studies, there were a total of 71 155 participants with 388 288 person-years of observation, and 9142 deaths. The weighted average all-cause mortality rate was 2.35% per annum, with a 95% CI of the average rate estimated as between 2.03% and 2.68% per annum.

AIDS mortality

There was wide variation between studies in the annual mortality rate attributed to HIV/AIDS (see table 1). The weighted crude HIV/AIDS mortality rate from these studies was 0.78% per annum and the 95% confidence interval was 0.58% to 0.97% per annum.

Non-AIDS mortality

The median non-AIDS mortality rate was estimated to be 1.08% per annum (see table 2). The lower limit of this estimate (using the methods described above) was 0.58% per annum; the upper limit was 1.58% per annum.

DISCUSSION

The current paper derived weighted mortality rates based upon cohort studies that comprised a total of 179 885 participants involving 1 219 422 person-years of observation and 16 593 deaths. The weighted crude AIDS mortality rate from studies that reported AIDS deaths was approximately 0.78% per annum. The median estimated non-AIDS mortality rate was 1.08% per annum. The lower limit of this estimate was 0.58% per annum, and the upper limit was 1.58% per annum. Hence, it is estimated from the existing cohort studies that among IDUs, non-AIDS deaths outnumber AIDS deaths by around 40%.

Methodological caveats

A number of potential sources of uncertainty need be acknowledged in these estimates. First, environmental, cultural, or behavioural factors—which are also likely to

Table 2 Estimates of mortality per 100 person-years among injecting drug users

	All-cause mortality	AIDS mortality§	Non-AIDS mortality
Lower range*	1.3607	0.7778	0.5829
Upper range†	2.3544	0.7778	1.5766
Median estimate‡	1.8576	0.7778	1.0798

*Lower estimate: weighted crude mortality rate obtained when all cohort studies were included.
†Upper estimate: weighted crude mortality rate obtained when only cohorts reporting numbers of AIDS deaths included.
‡Median estimate: median of these two estimates.
§Estimate produced from cohort studies that reported AIDS mortality.

interact—probably affect mortality rates in different countries, and even different cities in the same country. The risk of contracting HIV through injecting drug use is greatly reduced by providing sterile injecting equipment, and the use of such equipment will be affected by attitudes towards needle sharing. Furthermore, in countries without needle and syringe programmes (NSP), more IDUs are at risk of contracting HIV (and therefore dying of AIDS related causes) than in countries where NSP are provided, assuming a similar prevalence of other risk factors for HIV transmission.[72] For example, it has been estimated that between 10 000 and 25 000 HIV infections in the US could have been prevented if needle exchange programmes were implemented as they had been in Australia.[73]

Second, the availability of drug treatment programmes and medical care may affect mortality rates. The variation in mortality rates that results from differences in the interactions of determinants of mortality complicate comparisons of mortality rates in cohort studies done in different countries. For example, van Ameijden *et al*[45] compared mortality in cohorts of heroin users in Amsterdam and Baltimore. They found Amsterdam drug users had an overdose/suicide mortality rate approximately twice that of their counterparts in Baltimore. This was despite the fact that a greater proportion of users in Amsterdam were in methadone maintenance treatment which has been shown to reduce the risk of overdose. This finding contrasts with a previous finding of the same research group, which attributed lower mortality rates from infectious disease in Amsterdam to drug users having better access to primary health care in Amsterdam than in New York.[74]

Third, the vast majority of cohort studies of mortality among drug users have included people seeking treatment for their drug use. A small number of studies have compared mortality of drug users while in and out of treatment.[46 61 65 75–77] These studies have found that the relative risk of death while in treatment varied from less than 0.2 to 0.8 compared to those out of treatment, with a mean of approximately 0.4. It is difficult to estimate which proportion of users have been in treatment for which periods of time in the cohort studies examined here; it is typical for users to cycle in and out of treatment, and information on time in and out of treatment is simply not recorded in the studies.

Fourth, injecting *opioid* users are overrepresented in the cohort studies by comparison with cocaine and other stimulant users. The few studies that report separate data on problem illicit opioid and stimulant use suggest that mortality is higher among opioid users,[34] probably because of the greater risk of fatal overdose from opioids. Stimulant users, by contrast, may be at higher risk of contracting diseases from blood borne viruses such as hepatitis B and C from sharing injection equipment because they inject more frequently.[78 79] They may also be more likely to engage in sex for drugs.[80–82] Because of the limited data our mortality estimates had to be calculated using data pooled from users of all drugs.

Fifth, applying direct measures of mortality from cohort studies in developed countries to populations in developing countries is especially problematic. Developing countries generally have all-cause mortality rates that are significantly higher than the developed countries in which most cohort studies are conducted.[83] It may be that there is less of a differential in mortality rates between the general population and injecting drug users in developing countries. For this reason, crude mortality rates have been presented here. There are also a number of other factors that mean we need to be careful about extending these estimates from developed countries to populations of IDUs in developing countries. Differences in drug purity may exist between developed countries and developing countries: many of the developing countries with increasing IDU populations are situated close to the source countries of the drugs they inject (for example, Iran and Thailand are close to the Golden Crescent and Golden Triangle respectively), which may mean that overdose risks are higher because the drugs are of higher purity than the more distant developed countries. Further, lower hygiene levels surrounding drug injection may also contribute to increase septicaemia among IDUs in developing countries that do not have widespread provision of clean injecting equipment. The latter, however, is unlikely to contribute to greatly increased mortality because of the typically very low rates of *mortality* due to this in the existing literature, even in countries without good NSP provision.[54 57]

Sixth, the majority of cohort studies identified for this project were conducted before the HIV epidemic began to affect mortality among IDUs. Changes in the epidemiology of HIV and other drug related conditions since these studies were conducted may reduce the validity of using prevalence or incidence data to predict mortality. In some developed nations, for example, the incidence of HIV and AIDS may be declining but the large number of prevalent cases may still produce a high burden of mortality.[84 85] Conversely, countries that are still in the early stages of the epidemic may have a high incidence of HIV/AIDS cases that have not yet begun to contribute to mortality. In either case, mortality estimates based on the number of incident cases may be inaccurate, for very different reasons. Further, it is possible that AIDS related deaths may have been misdiagnosed even in countries with relatively established AIDS epidemics, which would lead to an underestimate of the proportion of all-cause mortality due to this cause.

Seventh, highly active antiretroviral therapy (HAART) has been demonstrated to reduce not only HIV viral load but also AIDS related mortality.[86] This means that mortality rates due to AIDS since the introduction of HAART in the mid 1990s will have been lowered as a result.[87] Considerable care needs to be taken when considering the implications of the current data for countries in which HAART is not widely available (or not available to IDUs), because the mortality rates in many of the cohort studies used in this review include the period following the introduction of HAART.

The reduction in AIDS related mortality among IDUs may not be as large as the overall reductions due to HAART that have been demonstrated in cohorts of HIV positive people. HIV positive IDUs are less likely to be enrolled in HAART than non-IDUs;[88] and even when maintained on HAART, they have been shown to have higher rates of mortality than non-IDUs.[89–91] There are multiple potential explanations for this finding: IDUs are less likely to adhere to the strict treatment regime;[92 93] they are more likely to be co-infected with hepatitis C,[94–96] which independently increases the risk of mortality among HIV positive people even when maintained on HAART;[97] and IDUs have been found to have a

lower virologic response to HAART than non-IDUs.[98] In summary, the AIDS mortality rate is likely to be higher in developing countries without widespread HAART availability to IDUs, but the extent of this increased mortality rate may not be the same for IDU as for non-IDU HIV positive populations in these same countries compared with countries that provide HAART.

Finally, it is important to acknowledge the possibility that AIDS related deaths were not accurately diagnosed as such. This would lead to an underestimate of the mortality rates attributable to AIDS. It is unclear to what extent this bias will have affected the rates we have obtained, but the extent of the bias would probably have been greater in earlier cohorts. In prospective cohorts of IDU however, it seems reasonable to assume that the investigators would have been sensitive to these possibilities and examined causes of death carefully to avoid such bias.

Despite the limitations of existing cohort studies, however, they are the most robust form of epidemiological evidence on the relation between illicit drug use and mortality. Cohort studies therefore provide the best basis on which to estimate risk and identify mortality outcomes. The use of annual mortality rates derived from studies of illicit drug users in developed countries may *underestimate* mortality in developing countries. By contrast, applying standardised mortality ratios from the cohort studies to developed societies may *overestimate* the mortality rate of drug users in developing countries (which already have higher mortality rates in general), since it is probable that the higher the general mortality rate in any given country, the lower will be the SMR for illicit drug users in that country.[99] In the present case, mortality rates have been used, so it is likely that there may be a slight underestimate of IDU related mortality in developing countries as a result.

Research priorities

There is a need for more rigorously designed prospective studies of mortality and morbidity among problem illicit drug users in developing countries. Such studies are especially needed in countries that have high rates of HIV infection among injecting drug users, and which have experienced substantial increases in injecting drug use in recent years. There is also a need for cohort studies of IDU who are *not* in treatment, since there is evidence that rates of mortality may be higher among this group. Recent work in countries such as Thailand[100] will doubtless provide estimates in the coming years and will be an important addition to the literature.

Better data collection systems need to be put in place to collect data on drug related mortality; to improve the consistency of procedures used to identify and register drug related deaths; to monitor mortality by drug type, especially in developing countries and countries with high HIV prevalence; and measure the coverage and nature of services in place to reduce mortality.

CONCLUSIONS

There is a considerable amount of data from cohort studies of illicit drug users that can be used to estimate the rate or mortality among this group. Unfortunately, most of these studies have been conducted in developed countries on problem opioid users and many were conducted before the AIDS pandemic among IDUs. A priority for future research must be to better assess mortality among illicit drug users in developing countries and, in particular, to examine the extent to which the findings of studies conducted in developed countries are applicable to developing countries. Furthermore, much of this research has been based on samples of people entering treatment for drug related problems. Further work is needed to quantify mortality among IDUs who are *not* in treatment. Nonetheless, it is clear from the existing cohort studies that IDUs have a greatly increased risk of premature death. Mortality due to AIDS certainly forms a significant part of that increased risk, but multiple causes of the increased mortality exist.

ACKNOWLEDGEMENTS

The work involved in the collection of much of the mortality data from cohort studies was completed in collaboration with Dr Michael Lynskey as part of the Comparative Risk Assessment for Illicit Drugs in the 2000 Global Burden of Disease study.[4]

AUTHORS' CONTRIBUTIONS

Louisa Degenhardt contributed to the conceptualisation of this paper, conducted the bulk of the analysis of the data for this study, and wrote sections of the paper. Wayne Hall contributed significantly to the writing of this paper and the conceptualisation of the study. Matthew Warner-Smith was involved significantly in the early stages of the work collecting data from cohort studies, conceptualising the study, and made comments on the paper.

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Competing interests: none.

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